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The Mutation Load in an African Population. I. An Analysis of Consanguineous Marriages in Nigeria

AJOVI B. SCOTT-EMUAKPOR[1]

Consanguineous marriages have been studied in several populations primarily to appraise the mutation load in man. No such study has yet been reported for an African population. The purpose of this paper is to estimate the approximate number of rare recessive genes present in an average Nigerian, based on the increase of miscarriages, deaths, and abnormalities in consanguineous marriages.

Scientific investigations of genetic consequences of consanguineous marriages began more than a century ago with the work of Bemiss [1]. Mitchell [2] studied all marriages in a European population in order to detect the consanguineous matings. His technique has proven to be quite successful. More contemporary studies of consanguinity include the work of Sutter and Tabah [3] on a French population, Böök [4] on a North Swedish population, Slatis et al. [5] on a U.S. (Chicago) population, Freire-Maia and co-workers [6, 7] on a Brazilian population, and Schull and Neel [8] on Japanese populations. Controls for these studies were either chosen randomly from the population or from among relatives of the consanguineous spouses. Freire-Maia and Azevedo [9] point out that erroneous estimates of the mutation load result from use of inappropriate controls. The present study utilizes a unique polygamous mating system in Nigeria in which both consanguineous and nonconsanguineous wives live in the same household.

SUBJECTS AND METHODS

Data for this study were collected from Oka Akoko, a community of approximately 60,000 Yoruba-speaking Nigerians in the Western State of Nigeria. The population practices polygamy and preferentially includes both consanguineous and unrelated spouses within each household.

The inclusion of at least one close relative as a wife in each household is required by custom, and most of the men conform. The relationship of the consanguineous spouse ranges from half first cousin once removed to niece. The population is therefore unusual in that each family or household provides its own control, thus removing most bias associated with differences in background, socioeconomic status, and health conditions.

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[1] Departments of Zoology and Chemical Pathology, University of Ibadan, Ibadan, Nigeria. Present address: Department of Human Development, Michigan State University, East Lansing, Michigan 48824.

During the interview with each household, a brief description of the relationship between the consanguineous spouses was made in the form of a pedigree. Families were asked the number of wives in the household, their names, and their relationship to the man of the house. The following questions were asked of each wife: number of pregnancies, live births, and stillbirths; length of gestation before miscarriage or abortion; neonatal and childhood deaths including cause and age; and abnormalities (not including polydactyly) and ailments among living children.

RESULTS

The eight types of consanguineous marriages encountered in this study and their frequencies are shown in table 1. Each type has a similar number of controls

TABLE 1

TYPES OF CONSANGUINITY

Type	Inbreeding Coefficient (F)	No. Consanguineous Marriages (%)	No. Control Marriages
Uncle-niece	1/8	23 (9.6)	22
Half uncle–niece	1/16	60 (25.0)	52
Uncle–grand niece	1/16	4 (1.7)	3
First cousin	1/16	21 (8.8)	18
Half first cousin	1/32	40 (16.6)	44
Half uncle–grand niece	1/32	23 (9.6)	31
First cousin once removed	1/32	8 (3.3)	7
Half first cousin once removed	1/64	61 (25.4)	52
Total	...	240	229

from the nonconsanguineous marriages. Interviews were conducted in 150 households and involved 469 wives. Thus, on the average, each man was married to about three wives. Of the 469 spouses, 240 (51%) were consanguineous.

Pregnancies and Live Births

The number of pregnancies for consanguineous and control spouses was 868 (average, 3.6 per spouse) and 627 (average, 2.7 per spouse), respectively.

There were 778 live births (four instances of twinning) for the consanguineous spouses (an average of 3.2 per woman) and 589 live births for the control spouses (an average of 2.6 per woman). The ratio of live births per wife is 16:13 in favor of the consanguineous spouses; however, this ratio is reduced when compared to that of pregnancies per wife.

Spontaneous Abortions

A total of 94 spontaneous abortions occurred among the 868 pregnancies of consanguineous spouses, for an average of about 0.4 per wife and a frequency of .1082 (table 2). For the 229 control spouses, 38 occurred among the 627 total pregnancies, or approximately 0.16 per spouse (frequency, .0606). Spontaneous

TABLE 2

SPONTANEOUS ABORTIONS IN CONSANGUINEOUS SPOUSES AND CONTROLS

Type of Marriage	Consanguineous			Control			
	Abortions	Pregnancies	Frequency	Abortions	Pregnancies	Frequency	Difference
Uncle-niece	14	89	.1573	6	72	.0833	.0740
Half uncle-niece	21	220	.0954	9	154	.0584	.0370
Uncle-grand niece	1	19	.0526	0	6	.0000	.0526
First cousin	12	87	.1379	2	45	.0444	.0935
Half first cousin	17	157	.1082	9	128	.0703	.0379
Half uncle-grand niece	9	73	.1233	5	70	.0714	.0519
First cousin once removed	4	26	.1538	0	20	.0000	.1538
Half first cousin once removed	16	197	.0812	7	132	.0530	.0282
Total	94	868	.1082	38	627	.0606	.0476

abortions are therefore more than twice as frequent among consanguineous spouses compared to control spouses, the difference being significant at the .01 level ($\chi^2 = 8.67$, 1 df). The highest frequency among the consanguineous spouses was in uncle-niece matings, the group with the highest inbreeding coefficient. The lowest incidence was in uncle–grand niece marriages. Marriages between half first cousins once removed, the group with the lowest inbreeding coefficient, have an incidence of .0812, which is the second lowest among the consanguineous marriages. It is worth noting that the controls in households with uncle-niece matings also show the highest incidence of spontaneous abortion. This finding is difficult to explain.

Neonatal Deaths

Neonatal death is here defined as death within the first 2 months of life. Twenty such deaths occurred among the 778 children of consanguineous matings, for a frequency of .0257 (table 3). Among the 589 children of control matings, only two deaths were reported for half uncle–niece control marriages (frequency, .0034). Among the children of consanguineous matings, neonatal deaths were reported for all types of marriages except uncle–grand niece and first cousins once removed, where the number of births are comparatively few. Uncle-niece marriages had one of the highest frequencies of neonatal deaths.

Childhood Deaths

Among the children of consanguineous matings, 128 deaths were recorded from a total of 758 living children for a frequency of .1688 (table 4). The frequency of childhood deaths among children of controls (.0936) is almost half that among children of consanguineous matings; the difference is significant at the .01 level ($\chi^2 = 12.21$; 1 df). Children of uncle-niece control marriages show the same

TABLE 3

FREQUENCY OF NEONATAL DEATHS AMONG CHILDREN OF CONSANGUINEOUS SPOUSES AND CONTROLS

Type of Marriage	Consanguineous			Control			Difference
	Deaths	Live Births	Frequency	Deaths	Live Births	Frequency	
Uncle-niece	3	75	.0400	0	66	.0000	.0400
Half uncle-niece	8	199	.0402	2	145	.0137	.0265
Uncle-grand niece	0	18	.0000	0	6	.0000	.0000
First cousin	3	75	.0400	0	43	.0000	.4000
Half first cousin*	2	142	.0141	0	119	.0000	.0141
Half uncle-grand niece*	1	66	.0151	0	65	.0000	.0151
First cousin once removed	0	22	.0000	0	20	.0000	.0000
Half first cousin once removed	3	181	.0165	0	125	.0000	.0165
Total	20	778	.0257	2	589	.0034	.0223

* Includes two instances of twinning.

TABLE 4

FREQUENCY OF CHILDHOOD DEATHS AMONG CHILDREN OF CONSANGUINEOUS SPOUSES AND CONTROLS

Type of Marriage	Consanguineous			Control			Difference
	Deaths	No. Children	Frequency	Deaths	No. Children	Frequency	
Uncle-niece	12	72	.1666	11	66	.1666	.0000
Half uncle-niece	29	191	.1518	9	143	.0629	.0889
Uncle-grand niece	4	18	.2222	0	6	.0000	.2222
First cousin	16	72	.2222	5	43	.1163	.1059
Half first cousin	28	140	.2000	15	119	.1260	.0740
Half uncle-grand niece	13	65	.2000	5	65	.0769	.1231
First cousin once removed	4	22	.1818	2	20	.1000	.0818
Half first cousin once removed	22	178	.1235	8	125	.0640	.0595
Total	128	758	.1688	55	587	.0936	.0752

frequency of childhood death as those of the consanguineous marriages. Equally of interest is the fact that children of marriages between half first cousins once removed (the lowest inbreeding coefficient) show the lowest frequency of childhood deaths among the various types of consanguineous marriages. No childhood deaths were reported for uncle–grand niece control marriages, probably because of the small number of children involved.

Abnormalities

Among living children of control marriages, no abnormalities were reported; however, among 630 living children of consanguineous marriages, 10 abnormalities were observed for a frequency of .0158 (table 5). Apart from one case of acrocephaly and two cases of apparent mental retardation, all of the abnormal children are congenital cripples, probably the result of some form of cerebral palsy. Since childhood immunizations are absent in this area, polio cannot be ruled out completely as a cause. However, since there were no congenital cripples among the 532 living children of controls, it would seem that polio is not likely responsible.

TABLE 5

FREQUENCY OF ABNORMALITIES AMONG LIVING CHILDREN OF CONSANGUINEOUS SPOUSES AND CONTROLS

Type of Marriage	Consanguineous			Control			Difference
	No. Abnormal	No. Living	Frequency	No. Abnormal	No. Living	Frequency	
Uncle-niece	2	60	.0333	0	55	.000	.0333
Half uncle-niece	1	162	.0061	0	134	.000	.0061
Uncle-grand niece	1	14	.0714	0	6	.0000	.0714
First cousin	0	56	.0000	0	38	.000	.0000
Half first cousin	0	112	.0000	0	104	.0000	.000
Half uncle-grand niece	4	52	.0769	0	60	.000	.0769
First cousin once removed	0	18	.000	0	18	.000	.000
Half first cousin once removed	2	156	.0128	0	117	.000	.0128
Total	10	630	.0158	0	532	.000	.0158

DISCUSSION

In analyzing the data, the concept of lethal equivalents advanced by Morton et al. [10] was employed. Their estimates of the number of lethal equivalents are derived by assuming that the differences in the rates of miscarriages, neonatal and childhood deaths, and abnormalities between the consanguineous and control populations are an expression of lethal or abnormal genes of varying degrees of penetrance. It is possible to calculate the number of heterozygous deleterious genes carried per person using this concept. Since the present data involve eight types of consanguinity and their controls and the value of equivalents differ for each type of consanguinity, they have been dealt with separately. Table 6 gives the estimates of equivalents acting at different times during pre- and postnatal life for the various types of consanguinity.

Slatis et al. [5] have shown that for first cousin data, the homozygous recessive genes reflect 1/32 of those present in an average common ancestor instead of

TABLE 6

ESTIMATION OF LETHAL AND ABNORMAL EQUIVALENTS ACTING AT DIFFERENT TIMES IN PRE- AND POSTNATAL LIFE USING SEPARATE CONTROLS

Type of Consanguinity	Abortion	Still-birth	Neonatal Death	Childhood Death	Abnor-mality	Total
Uncle-niece	1.18	0.00	0.64	0.00	0.53	2.35
Half uncle–niece	1.18	0.00	0.85	2.84	0.20	5.08
Uncle–grand niece	1.68	0.00	0.00	7.11	2.28	11.07
First cousin	2.99	0.00	1.28	3.39	0.00	7.66
Half first cousin	2.43	−0.53	0.90	4.74	0.00	7.53
Half uncle–grand niece	3.32	0.00	0.97	7.88	4.92	17.09
First cousin once removed	9.86	0.00	0.00	5.23	0.00	15.09
Half first cousin once removed	3.61	0.00	2.11	7.62	1.64	14.98

NOTE.—Average total equivalents = 10.10 ± 4.95 (SD).

1/16 (the inbreeding coefficient) as suggested by Penrose [11]. Consequently, for the uncle-niece data ($F = 1/8$), the homozygous recessive genes reflect 1/16 of those present in an average common ancestor. Therefore the number of lethal or abnormal equivalents carried by an average individual may be obtained by multiplying the difference in frequency at the various times in pre- and postnatal life between the consanguineous and control group by a factor of 16.

The difference in frequency of spontaneous abortions between uncle-niece consanguineous marriages and controls is .0740 (table 2). Multiplying this by a factor of 16 yields 1.18, the number of lethal equivalents per person that would act at this period of development (table 6). Stillbirths were absent in both groups. Neonatal deaths show a difference of .0400 between uncle-niece marriages and controls (table 3), for a lethal equivalent of 0.64. There was no difference in the frequency of childhood deaths between the two groups (table 4), implying no action of lethal equivalents. The observed increase in the incidence of abnormalities among the consanguineous group is .0333 (table 5), indicating an abnormal equivalent of 0.53. Thus the total number of lethal equivalents per person using data from uncle-niece marriages is 1.82 and that of abnormal equivalents per person is 0.53, for a total of 2.35 lethons (used here to mean the total number of fully penetrant genes showing deleterious effects).

Using the above procedure, the equivalents for the other seven types of consanguineous matings were calculated and are shown in table 6. Note that stillbirths show a negative effect; only a single case of stillbirth was found in this study. Also of interest is that the highest number of abnormal equivalents was 4.92 for half uncle–grand niece marriages ($F = 1/32$).

Based on these calculations, the average common ancestor of the children of consanguineous marriages carries approximately 10.10 ± 4.95 (SD) detrimental gene equivalents, which should be similar to the number carried by an average member of the present population. There appears to be an inverse relationship between the mutation load (as measured by the total equivalents or lethons) and the degree of inbreeding (as measured by the inbreeding coefficient). Thus, uncle-niece data with the highest inbreeding coefficient showed the lowest number of lethons, while half first cousins once removed, with the lowest inbreeding coefficient, had the third highest number of lethons. This relationship has been implied in the data of Freire-Maia and colleagues [6, 7, 9].

The average number of equivalents estimated from this work is rather high compared to the value of 4.5 reported by Slatis et al. [5] in their Chicago study and that of 5.88 estimated from Böök's data [4]. However, by pooling the control data, new frequency values for controls are obtained (spontaneous abortions, .0606; stillbirths, .0016; neonatal deaths, .0034; childhood deaths, 0938; abnormalities, .00) which yield an average number of equivalents of 8.71 ± 3.92 (table 7). Slatis [12] derived a formula by which he obtained a value of approximately 8 as the number of heterozygous deleterious genes carried per person. Thus the value derived in this study, using pooled control data, comes within Slatis's calculation.

TABLE 7

ESTIMATION OF LETHAL AND ABNORMAL EQUIVALENTS ACTING AT DIFFERENT TIMES IN PRE- AND POSTNATAL LIFE USING POOLED CONTROL DATA

Type of Consanguinity	Abortion	Stillbirth	Neonatal Death	Childhood Death	Abnormality	Total
Uncle-niece	1.55	—0.05	0.59	0.59	0.53	3.78
Half uncle–niece	1.11	—0.05	1.18	1.86	0.19	4.29
Uncle–grand niece	—0.26	—0.05	—0.11	4.11	2.28	5.97
First cousin	2.47	—0.05	1.17	4.11	0.00	7.70
Half first cousin	3.05	—0.05	0.68	6.80	0.00	10.48
Half uncle–grand niece	4.01	—0.05	0.75	6.80	4.92	16.43
First cousin once removed	5.96	—0.05	—0.22	5.63	0.00	11.32
Half first cousin once removed	2.64	—0.05	1.68	3.80	1.68	9.75

NOTE.—Average total equivalents = 8.71 ± 3.92 (SD).

This study shows an apparent negative relationship between consanguinity and stillbirth. Other studies on consanguinity have shown a slight positive relationship. Both positive and negative correlations would be expected if, in fact, stillbirths were not under genetic influence. Furthermore, in view of reports of high stillbirth rates among individuals of African descent in North America, a high stillbirth rate would have been expected in this study. One hesitates to draw conclusions from this study, however, because of possible misreporting of stillbirths as miscarriages. There is evidence that the subjects were reluctant to discuss children who were born dead.

With the exception of polydactyly, a number of congenital abnormalities are rarely seen in black populations. (A survey I conducted shows the frequency of polydactyly in Nigeria to be approximately .023.) The data presented here tend to confirm this because no abnormality was reported for the control group and only 10 cases for the consanguineous group (frequency, .0158). Abnormalities such as severe mental retardation which are frequently reported in other studies on consanguinity are absent in this study. This is most probably because such individuals die early due to inadequate medical management and hence appear as either neonatal or childhood deaths.

The average length of gestation before spontaneous abortions was 3.0 months in the consanguineous group and 5.51 months in the controls. Thus the lethal genes responsible for spontaneous abortions must be genes that act very early in development.

It was not possible to determine differences in the length of time between marriage and first pregnancy because what is known as "marriage" in Western societies very rarely occurs in most African societies until a child is expected or, sometimes, even after a child has been born. Information about the length of time of association before first pregnancy was fragmentary. Even information about the length of time between the first and second pregnancies was unreliable because in most, if not all, polygamous homes, some wives are preferred and naturally are more frequently pregnant than others. In this study, there is evidence that the consanguineous spouses were the preferred or favorite wives; consequently, consanguineous spouses showed, on the average, more pregnancies and live births than control spouses.

SUMMARY

An analysis of genetic load has been made for a Nigerian population that provides its own controls. The population practices polygamy and preferentially includes both consanguineous and unrelated spouses within each household. Thus the inbred sibships have controls with the same father, socioeconomic level, and conditions of health care. In this study, consanguinity ranged from uncle-niece ($F = 1/8$) to half first cousin once removed ($F = 1/64$). Miscarriages and childhood deaths as assessed by interviews of wives showed the greatest effects of consanguinity (i.e., the highest number of lethal equivalents or lethons). Consanguinity had some effect on neonatal deaths and serious abnormalities but no effect on stillbirths, which were rarely encountered in this population. The total number of heterozygous deleterious genes carried per person in this population was estimated to be 8.71 ± 3.92 (SD), which is not too different from estimates for several other racial groups.

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